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Astra makes quiet progress with respiratory pipeline

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In defending AstraZeneca against acquisition by Pfizer its executives pointed to oncology candidates such as the checkpoint inhibitor Medi4736 and lung cancer project AZD9291 as assets not fully valued by the American pursuer. Less well appreciated is Astra's portfolio of clinical-stage respiratory programmes, one of which appears to be the only project of its class to be tested in the clinic.

Given Astra's relative position in each therapy area, one might think that respiratory disease would draw more attention, even though oncology remains the hottest area of drug development. A focus on novel classes and severe disease – demonstrated by a licensing deal last week for an inhalable interferon for asthma – could allow Astra to expand even as growth in respiratory therapies flattens through the rest of the decade.

Ordinary and unusual

Astra executives themselves have made less of the respiratory disease pipeline, forecasting sales that are in line with consensus figures even as they pumped up the group's collective R&D (*Don't blame Soriot, he's just doing his job, May 7, 2014*). In some respects, it is somewhat ordinary: the phase III pipeline features some candidates in well-established classes like long-acting beta-2 agonists (LABAs) in the form of assets brought on board with the acquisition of Pearl Therapeutics (*Astra's Soriot finds hidden value in private assets, June 10, 2013*).

James Ward-Lilley, the UK group's vice-president of respiratory, inflammation and autoimmune disease, acknowledged that the respiratory group had not received the attention of the investor community in part because the potential payoff of a clinical gamble is not valued as highly. Established products like Symbicort and Pulmicort are recognised, and some analysts are pencilling numbers in for antibodies in respiratory disease, but there is more caution than with oncology assets.

"That should unwind as we get more data," he told *EP Vantage* in an interview.

A close look reveals that benralizumab could be one of the first antibodies on the market to treat uncontrolled asthma and advanced chronic obstructive pulmonary disease (COPD). As a phase III candidate it has a fairly weighty forecast to go along with its advanced clinical stage – sales of $429m in 2020. Its pivotal programme has enrolled 14,000 patients, so Astra will be hoping to see something more than a half-billion in sales to make its investment back (see table).

AstraZeneca's substantial investment in its respiratory pipeline					
	Trial ID	**Enrolment**	**Conditions**	**Agents**	**Pharma class**
Phase III	NCT01914757	2,014	Asthma	Benralizumab/ICS/LABA	Anti-IL-5 MAb
	NCT01928771	1,890	Asthma	Benralizumab/ICS/LABA	Anti-IL-5 MAb
	NCT02075255	240	Asthma	Benralizumab/ICS/LABA/oral corticosteroids	Anti-IL-5 MAb
	NCT01947946	1,410	Asthma	Benralizumab/medium-dose ICS/LABA	Anti-IL-5 MAb
	NCT02138916	3,486	COPD	Benralizumab	Anti-IL-5 MAb
	NCT02155660	4,850	COPD	Benralizumab	Anti-IL-5 MAb
Phase II	NCT01629667	302	Idiopathic Pulmonary Fibrosis	CAT-354 (tralokinumab)	Anti-IL-13 MAb
	NCT01902290	566	Asthma	Brodalumab	Anti-IL-17 MAb
	NCT02036580	30	Idiopathic Pulmonary Fibrosis	CAT-354 (tralokinumab)	Anti-IL-13 MAb
	NCT02054130	1,383	Asthma	AMG 157/ MEDI-9929	Anti-TSLP MAb
	NCT01238861	609	Asthma	Benralizumab	Anti-IL-5 MAb
	NCT01704495	1,148	Asthma	AZD5069	CXCR2 antagonist
Phase I	NCT01817855	34	COPD + healthy subjects	AZD7624	COPD agent
	NCT01890148	8	Asthma	AZD 5069	CXCR2 antagonist
	NCT01962935	57	COPD	AZD 4721 with AZD 5069	CXCR2 antagonist
	NCT02085473	60	Asthma (healthy subjects)	CAT-354 (tralokinumab)	Anti-IL-13 MAb
	Total	*18,087*			

Astra is in a race with its UK rival GlaxoSmithKline to premiere the first biological drug to treat asthma of eosinophilic origin. The target of benralizumab and mepolizumab is the same, interleukin 5, an activator of the eosinophils that mediate allergic and asthmatic response, high levels of which have been associated with disease severity.

“The biologicals opportunity is significant in severe asthma,” Mr Ward-Lilley said.

Pro-antibody

Phase IIb data presented at the American Thoracic Society meeting showed a statistically significant reduction in the asthma exacerbation rate and improvements in lung function for patients taking benralizumab in a year-long trial against placebo. Those patients had uncontrolled asthma an elevated baseline blood eosinophil counts.

Benralizumab, brought into the fold with the 2007 acquisition of MedImmune, is not alone in the Astra antibody pipeline for asthma and COPD. Tralokinumab, an IL-13 targeting agent that came with Cambridge Antibody Technology, is in phase II for COPD, and brodalumab, the Amgen-originated agent primarily targeting autoimmune disorders, is also in phase II. Another Amgen-originated antibody, AMG 157/MEDI-9929, is the only project targeting thymic stromal lymphopoietin in the clinic.

Given the array of treatments now available for mild asthmatics, including Astra's Symbicort and Pulmicort, opportunity in this disease is migrating towards the uncontrolled patients. But Mr Ward-Lilley notes that many patients with mild disease die because of exacerbations, providing a possible early entry point for advanced agents.

"We're awakening to the fact that some patients have profound eosinophilia with mild disease," he said.

More dealmaking

An interest in controlling exacerbations has driven Astra's interest in Synairgen's SNG001, an inhalable interferon beta that was secured for $7.25m up front and up to $225m in milestones. The target is viral respiratory tract infections that can trigger attacks.

This is one of the only clinical-stage interferon projects for respiratory diseases, and the only one that has received the validation of a big pharma partnership.

If Astra is alone in exploring interferon, it could be in a race once again with Glaxo along with Novartis in developing a CXC chemokine receptor 2 antagonist, a class that is hoped will act on neutrophil response in asthma. Mr Ward-Lilley characterised the targeting of neutrophils as an "intriguing hypothesis".

But the science has yet to answer the question: "Are they soldiers on the battlefield or observers?" he said.

The low-hanging fruit in respiratory disease have been picked, with effective treatments originating among the LABA, LAMA and corticosteroid classes. There are still some valuable niches, however, and Astra has not given up pursuing them, though by showing less exuberance about its lung drugs than its cancer drugs it risks downplaying an area that could remain strong.

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